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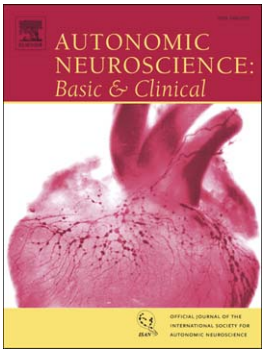

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Inflammation in CRPS: role of the sympathetic supply

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Abstract

Acute Complex regional Pain Syndrome (CRPS) is associated with signs of inflammation such as increased skin temperature, edema, skin colour changes and pain. Pro-inflammatory cytokines (tumor necrosis factor- α (TNF-α), interleukin-2 (IL-2), IL-1beta, IL-6) are up-regulated, whereas anti-inflammatory cytokines (IL-4, IL-10) are diminished. Adaptive immunity seems to be involved in CRPS pathophysiology as many patients have autoantibodies directed against β_2 adrenergic and muscarinic-2 receptors. In an animal tibial fracture model changes in the innate immune response such as up-regulation of keratinocytes are also found. Additionally, CRPS is accompanied by increased neurogenic inflammation which depends mainly on neuropeptides such as CGRP and Substance P.

Besides inflammatory signs, sympathetic nervous system involvement in CRPS results in cool skin, increased sweating and sympathetically-maintained pain. The norepinephrine level is lower in the CRPS-affected than contralateral limb, but sympathetic sprouting and up-regulation of alpha-adrenoceptors may result in an adrenergic supersensitivity.

The sympathetic nervous system and inflammation interact: norepinephrine influences the immune system and the production of cytokines. There is substantial evidence that this interaction contributes to the pathophysiology and clinical presentation of CRPS, but this interaction is not straightforward. How inflammation in CRPS might be exaggerated by sympathetic transmitters requires further elucidation.

Keywords: inflammation, complex regional pain syndrome, sympathetic nervous system, cytokines

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1. Introduction

What is CRPS?

Complex Regional Pain Syndrome (CRPS) is a severe and often disabling syndrome, which develops in about 5% after trauma; most often distal radius fractures (Beerthuizen et al., 2012). CRPS may arise without (type I) or with a measurable nerve lesion (type II) and is defined as pain in combination with sensory, autonomic, trophic, and motor abnormalities (Harden et al., 2007; Marinus et al., 2011).

While recent research made clear that the longer CRPS persists without significant improvement the more central become neuroplastic changes in the CNS (Geha et al., 2008; Lewis and Schweinhardt, 2012), acute CRPS is characterized by an exacerbated posttraumatic inflammation. Accordingly, acute CRPS is associated with signs indicative of the classical hallmarks of inflammation such as increased skin temperature, edema, skin colour changes and pain. Moreover, trophic disturbances in hair and nail growth, high turnover osteoporosis and fibrosis of palmar aponeuroses or joint capsules might also be driven by inflammation (Harden et al. 2007). In chronic CRPS neuroplastic changes indicated by motor disorders (tremor, dystonia), allodynia or disturbances of body perception (diminished sensory discrimination, neglect-like phenomena, impaired visuospacial perception, body perception disturbances) (Janig and Baron, 2003; Maihofner et al., 2007; Moseley, 2005; Sumitani et al., 2007) prevail. In these patients changes of central autonomic pathways occur with diminished vasoconstrictor reflexes and asymmetric vasoconstrictor responses in CRPS (Cohen et al., 2012).

The posttraumatic inflammation related to CRPS

Human leukocyte antigens A3, B7 and DR2 are overrepresented in CRPS patients; DR2-positive patients had a worse outcome (Mailis and Wade, 1994). A3 and B7 belong to class I and DR2 to class II major histocompatibility complex antigens, and DR2 is associated with autoimmunity

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especially multiple sclerosis (Weiner et al., 1993). These initial findings suggested an immune mechanism and probably a genetic immune predisposition for CRPS (de Rooij et al., 2009). Subsequent investigations confirmed associations of different CRPS phenotypes with different HLA classes (van de Beek et al., 2003). More recently, an association with human leukocyte antigen-DQ8 again indicated a genetic component in CRPS with disturbed regulation of inflammation (van Rooijen et al., 2012). However, the relevance and reproducibility of the result has to be proven in further studies with more subjects.

Several studies have found a trauma-related activation of the immune system characterized by the up-regulation of pro-inflammatory cytokines in CRPS patients. In blood samples and cerebral spinal fluid from CRPS patients bradykinin (Blair et al., 1998) and pro-inflammatory cytokines (tumor necrosis factor- α (TNF-α), interleukin-2 (IL-2), IL-1beta, IL-6) were increased (Alexander et al., 2005), whereas anti-inflammatory cytokines (IL-4, IL-10) were diminished (Uceyler et al., 2007). Locally in the CRPS skin elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and tryptase were found (Groeneweg et al., 2008; Groeneweg et al., 2006; Huygen et al., 2002; Huygen et al., 2004; Kramer et al., 2011; Munnikes et al., 2005) as well as an increased number of dendritic cells (Calder et al., 1998). These cells are important for the initiation of innate immune responses (Segura and Amigorena, 2013). The increase in TNF-α compared to healthy controls occurs in patients with mechanical hyperalgesia (Maihofner et al., 2005). Taken together these results indicate that inflammation may cause sensitization of primary afferent nociceptors and subsequent central sensitization in nociceptive pathways

Inflammation not only plays an important role in CRPS, it is also important in neuropathic pain. In neuropathic pain models microglia in the spinal cord exert a regulatory influence on synaptic transmission from primary afferent to central projection neurons, release pro-inflammatory cytokines (Vitkovic et al., 2000) and show disease-associated changes (Banati, 2003; Cooper and Clark, 2012). After neuronal lesions microglia change their immunophenotype, proliferate and

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migrate, and possibly induce neuronal sprouting (Banati, 2002). T-lymphocytes also infiltrate the spinal cord in association with hyperalgesia (Cao and DeLeo, 2008; Costigan et al., 2009). The proportion of pro-inflammatory T1-helper cells and anti-inflammatory T2-helper cells is important: whereas T1 helper cells amplify hyperalgesia after nerve lesions, T2 helper cells prevent it (Moalem et al., 2004). CD4+ and FoxP3+- regulatory T-cells influence neuropathic pain, since FoxP3-knockout mice develop more neuropathic pain after nerve lesions (Austin et al., 2012). Conversely, mice without B- and T-cells (RAG $^{-/-}$) have less pain behaviour after nerve lesions than wild-type mice, indicating the importance of lymphocytes for the development of pain (Costigan et al. 2009). The lymphocyte balance between TH1/TH2 is changed in CRPS reflecting a diminished Th1-response, perhaps in an attempt to counteract CRPS inflammation (Kaufmann et al., 2007). As CRPS occurs mostly after fractures, it is interesting to note that fracture healing is improved in animals lacking an adaptive immune system (Toben et al., 2011). Although there is currently a lively discussion whether CRPS I is a neuropathic pain disorder or not, there should be no doubt that the longer CRPS persists, the more likely are neuropathic mechanisms like nerve fibre degeneration (Oaklander and Fields, 2009) or central reorganisation similar to phantom limbs (Maihofner et al. 2007).

Most of our knowledge about post-traumatic inflammation in relation to CRPS comes from the tibial fracture /casting rodent model developed by the group of Kingery and Clark (Guo et al., 2004; Li et al., 2010). They have been able to model many acute CRPS features in rats: pain, limb warmth, edema, loss of motor function and osteopenia. In fact, this model resembles acute changes as they occur in CRPS. It does not model all symptoms of CRPS, especially the symptoms seen in later stages. In the distal tissue they found increased signalling for cytokines such as TNF-α, IL-1ß and IL-6 on mRNA and protein levels, increased neuropeptide content (Substance P and calcitonin gene-related peptide (CGRP)) of the peripheral nerves (see also below), and IL-1ß-dependent up-regulation of NGF in affected skin (Li et al. 2010). In general, targeted antagonism of most of these molecules attenuated CRPS-like symptoms. There was also a role of mast cells in this rat model (Li

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et al., 2012) which constitute a major part of the cellular immune system in the skin and are an important source of histamine, cytokines, prostaglandins and proteases; in turn, these molecules sensitize nociceptors and facilitate inflammation.

Adaptive immunity seems also to be involved in CRPS pathophysiology, since in about 40% of CRPS patients auto-antibodies (Blaes et al., 2004; Kohr et al., 2009) are directed against β_2 adrenergic and muscarinic-2 receptors (Kohr et al., 2011). These findings led to the IRAM-hypothesis (IRAM = injury-triggered, regionally-restricted autoantibody-mediated autoimmune disorder with minimally-destructive course): Pre-existing circulating auto-antibodies may become pathogenic in the context of regional trauma (Goebel and Blaes, 2013), perhaps resulting in a relative shift in mediation of adrenergic effects from β- to α-adrenoceptors. Other signs of involvement of the immune system in CRPS are the improvement after intravenous immunoglobulin treatment (Goebel et al., 2010) and corticoids (Christensen et al., 1982; Kalita et al., 2006), and serological evidence for antecedent infections with chlamydia, parvovirus and campylobacter (Goebel and Blaes 2013; Goebel et al., 2005; Gross et al., 2007).

The neurogenic component of CRPS

Every inflammation has a neurogenic component. The visible inflammatory signs in CRPS are related to this neurogenic inflammation (Weber et al., 2001). Neurogenic inflammation is mediated by the release of neuropeptides (especially Substance P and CGRP) from peptidergic C-fiber terminals via axon reflex mechanisms (Holzer, 1998; Schmelz and Petersen, 2001). Clinical symptoms are skin reddening due to vasodilation (probably CGRP related), swelling due to plasma extravasation (probably substance P related) and hyperalgesia due to alterations in the excitability of sensory neurons by inflammation as described above (Birklein et al., 2000; Richardson and Vasko, 2002). Indeed, the neuropeptide CGRP is increased in CRPS serum samples (Birklein et al., 2001). Substance P induces plasma extravasation. In CRPS, this plasma extravasation was

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measured by scintigraphy with indium-111 labelled immunoglobulin G as a marker of increased vascular permeability for macromolecules in the affected limb (Oyen et al., 1993). Furthermore, after electrical stimulation of peptidergic C-fibres, Substance P (SP) related plasma protein extravasation was detected in CRPS-affected but not control skin (Weber et al. 2001). Downstream, SP might be a key for mast cell degranulation and release of inflammatory mediators which, in turn, could up-regulate SP in peptidergic nerves (Wei et al., 2009; Woolf et al., 1994). Accordingly, when SP is infused directly into the CRPS skin it is more effective in inducing plasma extravasation (Leis et al., 2003).

Sympathetic nervous system disturbances in CRPS

Initially most patients have a warm and red limb as a sign of inflammation. In chronic CRPS temperature and perfusion of the affected limb are consistently lower than those of the contralateral limb, resulting in a cool moist limb (Wasner et al., 2001). Paradoxically, though, norepinephrine levels were found to be lower in the affected than contralateral limb of CRPS patients (Drummond et al., 1991; Harden et al., 1994). Biopsies taken from people with chronic CRPS-1 suggest that this apparent paradox is most likely explained by increased density or responsiveness of alpha adrenoceptors in the skin (Drummond and Finch, 2004; Kurvers et al., 1996). Consistent with this, subcutaneous arteries from the affected side were less responsive to electrical stimulation, but showed a higher sensitivity to α_1-adrenoceptor stimulation (Kurvers et al., 1998). As a further sign of this adrenergic supersensitivity, the responsiveness of superficial dorsal hand veins to increasing doses of intravenous norepinephrine was greater in CRPS patients than controls (Arnold et al., 1993). Another broader sign of sympathetic imbalance is an increased heart rate, reduced heart rate variability, and an inability to protect cardiac output during orthostatic stress in CRPS, which is associated with CRPS duration, but not pain intensity (Terkelsen et al., 2012). Hyperhidrosis often occurs in CRPS. These patients not only have increased spontaneous sweating but also increased thermoregulatory sweating (Birklein et al., 1997) and sudomotor axon reflex sweating, which could

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be even elicited by α-adrenergic stimulation, which is in contrast to normal subjects (Birklein et al. 1997; Chemali et al., 2001).

Sympathetically maintained pain

In some animal models of neuropathic pain, the expression and density of α_2-adrenoceptors on damaged nerves is increased in association with heightened pain to adrenergic agonists (Birder and Perl, 1999; Perl, 1999; Sato and Perl, 1991). More physiologically, low frequency electrical stimulation of sympathetic neurons excites afferent C-fibers in chronically lesioned nerves (Häbler et al., 1987). The sympathetic nervous system also affects pain in inflammatory pain models. The animals show an increase in mechanical hyperalgesia after peripheral inflammation induced by formalin or spinal nerve inflammation by Freund´s adjuvant by adrenergic stimulation of α_1- (Hong and Abbott, 1996) or α_1- and α_2-adrenoceptors (Baik et al., 2003; Dogrul et al., 2006). However, in a small radio-ligand binding study in humans, the density of α_1-adrenoceptors was found to be greater in areas of hyperalgesia in CRPS patients than in pain-free controls, possibly reflecting a species or syndrome-specific difference (Drummond et al., 1996). These patients might have developed sympathetically-maintained pain.

A test of sympathetically-maintained pain (SMP) is the injection of norepinephrine, which is normally not painful, but becomes painful in certain patients with CRPS (Ali et al., 2000; Drummond and Finch 2004; Torebjork et al., 1995). Another sign of SMP is the increase of spontaneous pain and hyperalgesia evoked by sympathetic arousal during body or forehead cooling or by a startle stimulus (Baron et al., 2002; Drummond and Finch 2004; Drummond and Finch, 2013; Drummond et al., 2001). These patients report enhancement of pain by cold and stress. Therapeutically sympathetic blocks, which inhibit the sympathetic innervation of deep structures and the skin, can be used to alleviate pain (Baron and Maier, 1996; Schattschneider et al., 2006); the reduction of pain after sympathetic block is then consistent with SMP. A small uncontrolled trial found improvement of pain by the use of phenoxybenzamine, which induces a noncompetitive

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(irreversible) blockade of α_1- and α_2-adrenergic receptors (Inchiosa, Jr. and Kizelshteyn, 2008), and in another small study hyperalgesia improved after topical application of the α_2-agonist clonidine (clonidine blocks the release of norepinephrine from sympathetic nerve fibres, thereby decreasing activation of post-junctional α_1-adrenoceptors) (Davis et al., 1991). However, these were small uncontrolled studies, which need to be reproduced.

CRPS pain not only is influenced by peripheral autonomic changes but also by central changes (Janig and Baron 2003; Maihofner et al., 2004; Moseley, 2004) and by psychological factors which activate the stress system. Interestingly, patients developed CRPS more often if a fracture was preceded by stressful life events (Geertzen et al., 1998) or if they had an anxious personality (Dilek et al., 2012), and in some cases CRPS apparently developed spontaneously after a stressful life event (Grande et al., 2004; Pearson and Bailey, 2011). Consistent with involvement of the stress system in CRPS, plasma norepinephrine levels were higher in the contralateral unaffected limb of CRPS patients than controls, and the level of norepinephrine was found to be associated with scores on the Beck Depression Inventory and denial of psychological and emotional problems (Harden et al., 2004). MR-morphometry found grey matter atrophy in the right insula of CRPS patients, which is known to be involved in pain and autonomic function, and in the right ventromedial prefrontal cortex (VMPFC), which is involved in emotional decision-making (Geha et al. 2008), but whether this is a cause, consequence or incidental association with CRPS is unclear.

Interaction between the sympathetic nervous system and inflammation

Antigen presenting cells, such as dermal and epidermal dendritic cells, are a major source of the cytokine TNF-α and other inflammatory cytokines such as IL-1β and IL-12, which are key drivers of the pro-inflammatory cascade. Under normal conditions, norepinephrine inhibits the production of pro-inflammatory cytokines, including TNF-α, from these cells by acting on beta-adrenergic receptors (Goyarts et al., 2008). However, epidermal dendritic cells also express α_1-adrenoceptors

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(Seiffert et al., 2002), and these receptors additionally become expressed in inflamed lymphoid tissue and on circulating lymphocytes in patients with chronic inflammatory disease (Kavelaars, 2002). The expression of the α_{1A}-adrenoceptor subtype is driven by inflammatory mediators such as TNF-α and IL-1β (Heijnen et al., 1996). In turn, exposure to norepinephrine increases the production of the pro-inflammatory cytokine interleukin-6 (IL-6) in cells that express α_1-adrenoceptors (Heijnen et al. 1996; Perez et al., 2009; Rouppe, V et al., 2000).

Although these findings have to be confirmed in patients, the activation of aberrantly-expressed α_1-adrenoceptors on immune cells might contribute to chronic inflammation and pain in CRPS (Figure 1). TNF-α and other pro-inflammatory cytokines are elevated locally in the affected limb in the early stages of CRPS (Heijmans-Antonissen et al., 2006; Kramer et al. 2011).

An impact of sympathetic activity on the clinical course of chronic pain is not unique to CRPS. Sympathetic activity interferes with the clinical symptoms of immune-mediated arthritis; in these patients a reduction of sympathetic activity via sympathectomy or beta-blockers attenuates inflammation and hyperalgesia, and reduces proinflammatory mediators (IL-2, IL-17, TGF-beta) (Ebbinghaus et al., 2012; Koopman et al., 2011; Levine et al., 1986). Similar findings have been reported in animal models of CRPS. For example, in the distal tibia fracture model of CRPS, norepinephrine increased the production of the pro-inflammatory cytokine IL-6 and led to nociceptive sensitization via β_2-adrenergic receptors on keratinocytes. This effect was reversed after catecholamine depletion or an IL-6-antagonist (Li et al., 2013).

Postganglionic sympathetic neurons might modulate inflammatory reactions, either directly by releasing prostaglandins (Gonzales et al., 1991) or indirectly by releasing NGF from vascular smooth muscle cells (Tuttle et al., 1993) or the bladder (Schnegelsberg et al., 2010). As noted above, the sympathetic nervous system influences innate immunity via dendritic cells, which are modulated by adrenoreceptors: α_1- adrenoceptors stimulate and β_2-adrenoceptors inhibit dendritic cell migration and immune system activation (Maestroni, 2006). Indeed, the number of dendritic cells is increased in CRPS (Calder et al. 1998). Norepinephrine also induces proliferation of

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keratinocytes after limb fracture (Li et al. 2013). In turn, keratinocytes release IL-1β, IL-6, NGF, and TNF-α (Li et al. 2010), which sensitize nociceptors. This might be important in CRPS. For instance, Zhao et al. (Zhao et al., 2008) reported that sodium channel expression was increased in the keratinocyte layer of patients with CRPS and post herpetic neuralgia, and the beta-isoform of the inflammatory neuropeptide CGRP was found to be increased in keratinocytes both in CRPS patients and in animal models of pain (Hou et al., 2011).

Prostaglandins sensitize nociceptors (Gibbs et al., 2008), an effect which is also mediated by α_1-adrenoceptors on peripheral sympathetic endings and is reduced after sympathectomy (Lin et al., 2003). However, this has yet to be proven in CRPS.

The most recent findings of a sympathetic – inflammation link in CRPS relate to adaptive immunity. We found autoantibodies in CRPS patients which are agonistic on muscarinic acetylcholine m_2 receptors and β_2-adrenoceptors (Blaes et al., 2007; Kohr et al. 2011; Kohr et al. 2009). However, the clinical relevance of this finding has yet to be determined. The passive transfer of IgG antibodies from longstanding CRPS patients in mice changed motor functions (rearing behaviour, activity in rota rod test), but not autonomic symptoms (Goebel et al., 2011).

The impact of the SNS on neurogenic inflammation in CRPS

Besides injury-induced expression of novel adrenergic receptors, sprouting of sympathetic fibers occurs in the skin after chronic constriction injury of the sciatic nerve (Yen et al., 2006). In animal models of peripheral nerve lesions, sympathetic nerve sprouting was also detected in the dorsal root ganglia (DRG) and these sympathetic fibers formed baskets around large primary neuronal cell bodies (Gibbs et al. 2008; McLachlan et al., 1993; Pertovaara, 2006), of non-nociceptive A-fibers (Michaelis et al., 1996). In cultured DRG neurons, α_1-adrenoceptor stimulation increases cell excitability, whereas β-adrenergic stimulation reduces it (Pluteanu et al., 2002). However, the clinical relevance of that observation has to be proven because Häbler et al. found sympathetic-sensory coupling only in a minority of axotomized afferents after spinal nerve injury using

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unphysiologically high frequency electrical stimulation of the sympathetic chain (Häbler et al., 2000). Nerve injury increases the number of DRG cells responding to norepinephrine (Petersen et al., 1996), the proportion of DRG neurons expressing α_2-adrenoceptors (Birder and Perl 1999) and also the levels of α_1-adrenoceptor RNA (Maruo et al., 2006; Xie et al., 2001). To differentiate between ephaptic interactions between sympathetic efferents and nociceptive afferents or catecholamine-induced activation of nociceptive nerve endings, single fiber recording were performed in CRPS patients and a patient with SMP. The results showed that endogenously released catecholamines, but not ephaptic interactions mediated SMP (Campero et al., 2010; Jorum et al., 2007). Even in an animal model of chronic neuroma, no ephaptic transmission between postganglionic and afferent fibers existed (Blumberg and Janig, 1982). Under pathological conditions, the activation of postganglionic sympathetic neurons and release of norepinephrine during emotional arousal, stress, or cooling could directly excite primary sensory afferents (Baron et al. 2002; Donello et al., 2011; Drummond and Finch 2004). Subsequently, activation of peptidergic nociceptors may induce neurogenic inflammation characterized by pain, vasodilation and edema by neuropeptide release - as extensively described above.

Summary

The fact that sympathetic block might not generally be effective for CRPS treatment (Straube et al., 2010) indicates that the relationship between the sympathetic nervous system and pain in CRPS is not straightforward. Nevertheless, there is substantial evidence that inflammation and sympathetic disturbances contribute to the pathophysiology and clinical presentation of CRPS. Many studies demonstrate the impact of the sympathetic nervous system on pain and inflammation. However, since some of the hypotheses were obtained from models of neuropathic pain, they have to be proven in animal models of CRPS and also in humans. Additionally, the molecular mechanism whereby inflammation in CRPS might be exaggerated the sympathetic nervous system and its transmitters requires further elucidation.

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Future studies should solve the remaining questions:

1. Genetic predisposition: larger genetic studies have to confirm the association between certain genes linking the risk for developing CRPS to the immune system and the role of the translated proteins has to be established
2. Many studies found increased inflammatory mediators in CRPS patients. Some of these findings were obtained in the blood, but should be confirmed e.g. in skin biopsies and correlated to the clinical findings.
3. In CRPS patients autoantibodies have been found, directed against structures of the sympathetic nervous system. This should be confirmed from different patients' groups and the impact on pathophysiology should be evaluated.
4. Autonomic symptoms are frequent in CRPS. Some data indicate that adrenergic supersensitivity might be the cause but the final prove is missing.
5. We need an animal model resembling not only posttraumatic inflammation, but also chronic symptoms seen in CRPS patients. In this model the interaction between the immune system and the nociceptive and autonomic system have to be studies systematically.

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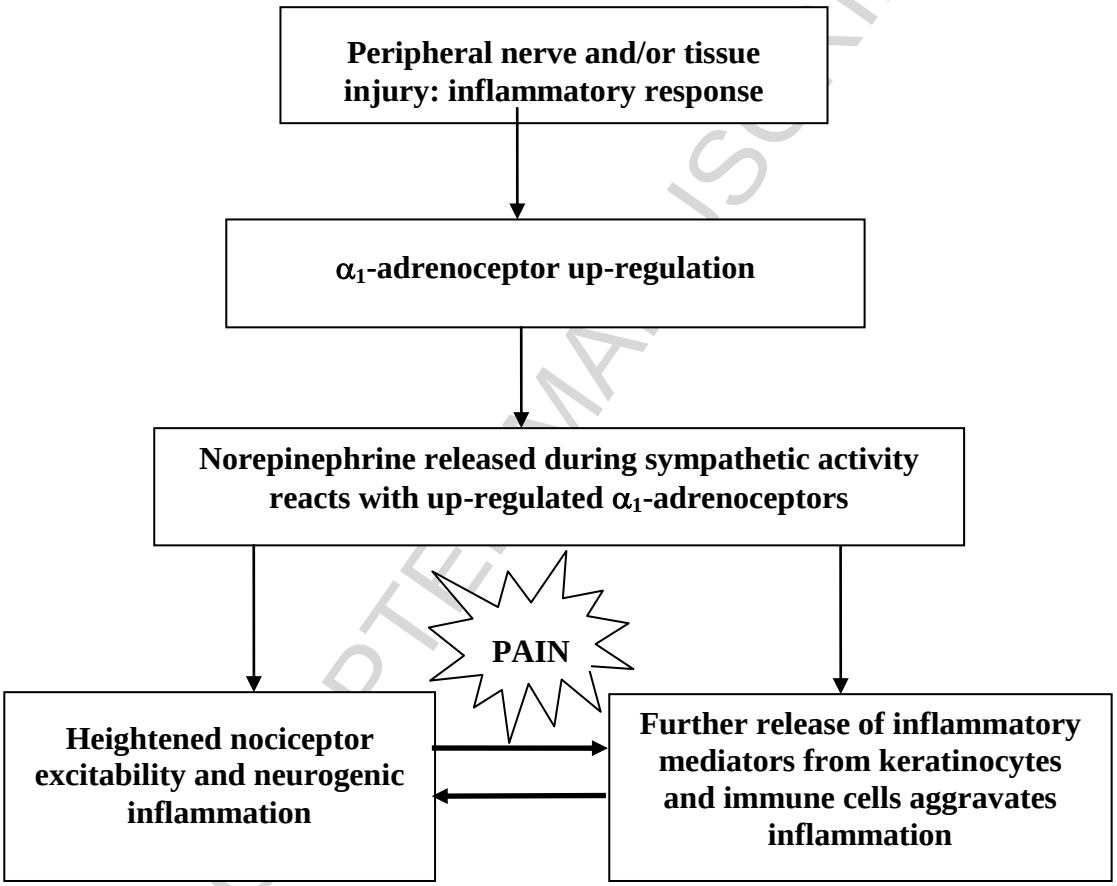
Fig. 1 Possible link between inflammation and sympathetic activity in inflammatory and neuropathic pain syndromes such as CRPS. Activation of up-regulated α_1-adrenoceptors on neurons, keratinocytes and immune cells may increase nociceptor excitability and aggravate inflammation and pain in an escalating cycle.



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